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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/328,296	06/08/1999	CLAY B. SIEGALL	9632-005	6564

7590 02/20/2004

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/328,296	SIEGALL ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-9,21-25,34,36,38,39,42-44 and 47-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-9,21-25,34,36,38,39,42-44 and 47-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. After review and reconsideration the finality of Paper No. 20 is withdrawn.

2. Claim 36 has been amended. Claim 35, drawn to a non-elected invention, remains withdrawn from consideration. Claims 1-9, 21-25, 34, 36, 38, 39, 42-44 and 47-91 are under consideration.

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 31, lines 12 and 33; page 32, line 5 and page 46, lines 1 and 3. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01

4. Claim 68 is objected to because it is drawn in part to canceled claims 40 and 41.

5. Claim 75 is objected to for reciting "which comprises which comprises".

6. Claims 8, 21-25 36, 44, 51-57, 60, 61, 66, 67, 73-78, 84, 85 and 90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8, 44 and 83 and dependent claims 51-54, 56, 57, 60, , 73-76, 84, 85 and 90 are rendered vague and indefinite by reference to a trade name, BLASTp, the object of which can be variable.

The metes and bounds of claims 44 and 83 and dependent claims 73-76, 84, 85 and 90 are unclear. Claims 44 and 83 recite "an amino acid sequence that comprises regions having at least 80% identity to SEQ ID NO:8, 9 and 10, respectively". The sequence are referred to collectively as SEQ ID NO:8-10, and thus the amino acid sequence must comprise all of sequence having at least 80% identity to SEQ ID NO:8-10, rather than an amino acid sequence having at least 80% identity to SEQ ID NO:8, 9 or 10. however, the presence of the term "respectively" impart the connotation that the amino acid sequence having 80% identity to SEQ

ID NO:8, 9 or 10 in the alternative is what is implied. For purpose of examination, all alternatives will be considered.

Claims 21 and 22 recite "in an amount effective for the treatment or prevention of cancer". Claims 23 and 24 recite "in an amount effective for activating or augmenting an immune response". Claim 36 recites "in an amount effective for the treatment or prevention of cancer or an immune disorder". Claims 25, 66, 77 and 78 are dependent on the aforesaid claims. The metes and bounds of said "amounts" cannot be set because the effective amounts would be a function of the size of the host, the route of administration and amount of pathological tissue present within the host. Further, it is unclear if this effective amount is applicable to the treatment or prevention of cancer or the augmenting of immune response in a single individual thus excluding effective amounts which would be administered to a plurality of individuals in need thereof.

Claims 55 and 56 recite "a fragment of an antibody containing the binding domain of the antibody". It is unclear if "the binding domain of the antibody" is referring to the domain which binds the Fc receptor, such as the human immunoglobulin constant domain, or if the domain is referring to the antigen binding domain.

7. Claims 6, 9, 22, 24 and 86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Claims 25, 38, 47-50, 52-54, 56-58, 66, 73, 78, 87, 88 and 91are rejected in part as they depend on the aforesaid claims. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's referral to the deposit of the hybridoma secreting the S2C6 antibody on page 58 of the specification is insufficient assurance that all the conditions of 37 CFR 1.801-1.809 have been met.

It is noted that the deposit was made under the provisions of the Budapest Treaty, therefore, the filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International

Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

8. Claims 21, 22, 25, 36, 66, 77 and 78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the claimed molecules and proteins in methods of treating cancer, does not reasonably provide enablement for methods of preventing cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The instant claims are drawn in part to methods of preventing cancer in a subject. This would require administration of the disclosed antibodies and molecules prior to the development of the cancers. However, there is no guidance in the specification for determining the appropriate time prior to the development of tumors to begin the therapy or for identifying patients who will develop cancers treatable by the claimed methods. Neither any art of record, nor the specification provides guidance with regard to the issues raised above. In view of the state of the art with regard to the prediction of cancer occurrence and the lack of teachings in the specification regarding how to select patients who will develop cancers treatable by the claimed methods and when to begin the claimed methods on said patients, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

9. Claims 36 and 61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the claimed antibodies and fusion proteins in methods of treating cancer, and/or activating or augmenting an immune response against a cancer antigen or cancer cell, does not provide enablement for a method of treating an immune disorder. When given the broade3st reasonable interpretation, "immune disorder" includes

autoimmune diseases such as Lupus Erythematosus, Addison's Disease, Graves' Disease, etc. There are no teachings in the specification or any art of record to support the notion that the administration of the claimed antibodies which bind to the CD40 receptor would result in a therapeutic effect for said autoimmune diseases. The teachings in the specification must be commensurate with the scope of the claims set forth, and one of skill in the art would not know how to treat broadly claimed immune disorders given the teachings of the specification. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the disclosed antibodies and fusion proteins in methods for the treatment of diseases other than cancer.

10. Claims 8, 36, 51-53, 56, 57, 69-73, 44, 74-76, 79, 83-85 and 90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A)As drawn to molecules without structural characterization

Claim 36 is drawn to a pharmaceutical composition comprising a molecule which binds CD40, which molecule increases the binding of CD40 ligand to cell surface CD40 by at least 45% in addition to CD40 ligand. Claim 69 is drawn to a molecule that binds to CD40 and increases the binding of CD40 ligand to CD40 on B cells by at least 45% and comprises a human immunoglobulin constant domain. Claim 70 embodies the molecule of claim 69 which is a protein. Claim 71 specifies that said protein is an antibody. Claim 72 is drawn in part to the molecule of claim 69 conjugated to a chemotherapeutic agent. Claim 79 specifies that the molecule of claim 72 is an antibody. Claims 36, 69 and 70 encompass a genus of molecules which bind to CD40 and increase the binding of CD40 ligand to CD40 receptor by at least 45%. When given the broadest reasonable interpretation claims 36 and 69 encompass molecules which are not proteins or antibodies, and which bind to an epitope of CD40 which is not the epitope to which the S2C6 antibody binds. The genus of claims 36, 69, 70-72 and 79 encompasses molecules and proteins which do not comprising antigen-binding portions of the S2C6 antibody and which do not bind to CD40 at the same epitope as the S2C6 antibody. Thus the genus of

molecules is highly variant encompassing structures which have unlimited structural alterations from the disclosed S2C6, and which have functional attributes which differ from the S2C6 antibody, such as binding to an CD40 epitope which differs from the S2C6 epitope. The disclosure of the S2C6 antibody does not adequately describe this genus of molecules because the structural and functional attributes of the genus vary from the structural and functional attributes of the S2C6 antibody. One of skill in the art would reasonably conclude that applicant was not in possession of the genus of antibodies on which the claimed method depends, therefore the methods lack adequate written description.

(B)As drawn to protein variants of SEQ ID NO:7 and protein variants of SEQ ID NO:8, 9 and 10.

Claim 8 is drawn to a protein comprising an amino acid sequence that comprises regions having at least 95% identity to SEQ ID NO:7, wherein said protein binds CD40 and has an immunoglobulin constant domain. Claims 44 is drawn to a protein comprising an amino acid sequence that comprises regions having at least 80% identity to SEQ ID NO: 8, 9 and 10, wherein said protein binds CD40 and has a human immunoglobulin constant domain. Claim 83 is drawn to a protein comprising an amino acid sequence that comprises regions having at least 80% identity to SEQ ID NO: 8, 9 and 10, wherein said protein binds CD40 and is a single chain Fv. Claim 84 embodies the protein of claim 83 which comprises SEQ ID NO:8, 9 or 10 rather than SEQ ID NO:8, 9 and 10. Claim 90 embodies the protein of claim 83 which is fused to bryodin. Claim 73 is drawn in part to the protein of claims 8 and 44 conjugated to a chemotherapeutic agent. Claim 74 embodies the protein of claim 44 which is an antibody. Claims 76 and 85 encompass the molecules of claims 44 and 83, respectively, wherein the molecule comprises at least two CDR sequences of SEQ ID NO:8, 9 or 10. Claim 84 embodies the protein of claim 83 which comprises SEQ ID NO:8, 9 or 10, rather than SEQ ID NO:8, 9 and 10. When given the broadest reasonable interpretation, the claims encompass a genus of proteins which vary from the structure of S2C6 and which encompass different functional attributes of S2C6 because the claims are not limited to those antibodies which bind to the same epitope of CD40 as S2C6. Thus the claims rely upon a genus of proteins which are structurally and functionally variant. The disclosure of the S2C6 antibody does not adequately describe this genus because the genus permits members having different structural and functional attributes

from the S2C6 antibody. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed genus of proteins and antibodies

11. Claims 1-3, 6-9, 21-24, 38, 39, 42-44, 47-66, 68-71, 74-76, 82 and 86-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Melief et al (U.S. Application 2003/0022860, priority to May 23, 1998, cited in a related Office action) in view of deBoer (U.S. 5,874,082, cited in a previous Office action).

Claim 1 is drawn to a molecule comprising SEQ ID NO:8, 9, and 10, which molecule binds CD40 and comprises a human immunoglobulin constant domain. Claim 2 embodies the molecule of claim 1 wherein the molecule comprises SEQ ID NO:7. Claim 55 embodies the molecule of claim 1 which is a fragment of an antibody comprising the binding domain of the antibody. Claim 43 specifies that the molecule of claim 2 further comprises SEQ ID NO:2. Claim 3 specifies that the molecule of claim 1 is an antibody. Claim 42 embodies the antibody of claim 3 which is humanized. Claim 6 embodies the molecule of claim 1 which is an antibody comprising a variable domain of S2C6 and a human immunoglobulin constant region. Claim 7 embodies the molecule of anyone of claims 1-3 which is purified. Claim 8 is drawn to a protein comprising an amino acid sequence that has at least 95% sequence identity to SEQ ID NO:7, which protein binds to CD40 and comprises a human immunoglobulin constant domain. Claim 9 is drawn to a protein which competes fro binding to CD40 with mAb S2C6, wherein said protein increases the binding ofCD40 ligand to the surface CD40 on B cells by at least 45% and comprises a human immunoglobulin constant domain. Claim 56 embodies the proteins of claims 8 or 9 wherein said protein is a fragment of an antibody comprising the binding domain of the antibody. Claim 21 is drawn to a pharmaceutical composition comprising a molecule comprising SEQ ID NO:2, 3, 4, 7, 8, 9 or 10 which binds to CD40 and increases the binding of CD40 ligand to CD40 on B cells by at least 45% and comprises a human immunoglobulin constant domain, wherein said molecule is present in an amount effective for the treatment and prevention of cancer. Claim 22 is drawn to a protein which competes for binding to CD40 with monoclonal antibody S2C6 as secreted by the hybridoma of ATCC Accession Number PTA-110, increases binding of CD40 ligand to CD40 on B cells by at least 45% and comprises a human constant domain, wherein said protein is present in an amount effective for the treatment and prevention

of cancer. Claim 23 is drawn to a pharmaceutical composition comprising a molecule comprising SEQ ID NO:2, 3, 4, 7, 8, 9 or 10 which binds to CD40 and increases the binding of CD40 ligand to CD40 on B cells by at least 45% and comprises a human immunoglobulin constant domain, wherein said molecule is present in an amount effective for activating or augmenting an immune response. Claim 24 is drawn to a protein which competes for binding to CD40 with monoclonal antibody S2C6 as secreted by the hybridoma of ATCC Accession Number PTA-110, increases binding of CD40 ligand to CD40 on B cells by at least 45% and comprises a human constant domain, wherein said protein is present in an amount effective for activating or augmenting an immune response. Claim 38 embodies the molecules of claims 1-6 in a pharmaceutically acceptable carrier.

Claim 44 is drawn to a protein comprising an amino acid sequence that comprises regions having at least 80% sequence identity to SEQ ID NO:8, 9 and 10, which protein binds to CD40 and comprises a human immunoglobulin constant domain. claim 74 embodies the protein of claim 44 which is an antibody. Claim 75 embodies the protein of claim 44 which comprises SEQ ID NO:8, 9 or 10. Claim 76 embodies the molecule of claim 44 which comprises at least 2 CDR sequences selected from the group consisting of SEQ ID NO:8, 9 and 10 .

Claim 69 is drawn to a molecule that binds CD40, increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45% and comprises a human immunoglobulin constant domain. claim 70 embodies the molecule of claim 69 which is a protein. Claim 71 embodies the protein of claim 70 which is an antibody. claim 82 embodies the molecule of claims 69 or 71 which comprises SEQ ID NO:8, 9 or 10.

Claim 86 is drawn to a molecule which competes for binding to CD40 with S2C6, wherein said molecule comprises at least 2 CDR sequences selected from the group consisting of SEQ ID NO:8, 9 and 10 and comprises a human immunoglobulin constant domain. Claim 87 embodies the molecule of claim 86 which is an antibody. Claim 88 embodies the molecule of claim 86 or 87 which comprises SEQ ID NO:8 and 10.

The specification teaches on page 5, lines 10-14 that said chimeric or humanized antibodies are constructed based on the variable chain and CDR regions of the S2C6 antibody and that SEQ ID NO:2 and 7 are the variable chains of said antibody and SEQ ID NO:3, 4, 8, 9 and 10 are the CDR of the S2C6 antibody. When given the broadest reasonable interpretation

the claims encompass the administration of a chimeric or humanized version of the S2C6 antibody.

Melief et al teach a method of treating cancer comprising the administration of CD40 binding molecules (abstract, claims 5-9, 11-13). Melief et al teach that the "triggering" of the CD40 in vivo can replace the requirement of a T-cell helper signal (examples 1 and 2 [0045]) and concludes that CD40 activation in the presence of tumor derived peptide reverses peripheral tolerance and results in tumor specific immunity (lines 22-24 of [0045]). Melief et al teach that the CD40 binding molecules include antibodies [0008] and that humanized antibodies are preferred for the treatment of human subjects [0030]. Melief et al teach that the administration of CD40-binding molecules enhances the efficacy of anti-cancer vaccines comprising tumor specific peptides [0047]. Melief et al teach FGK45 as a CD40 activating antibody (line 5 of [0020]). Melief et al do not teach that administration of a humanized S2C6 antibody for the treatment of cancer.

DeBoar teaches that anti-CD40 antibodies known in the art [prior to the disclosure of deBoar] have a stimulatory effect on human B cells (column 2, lines 45-46 and 62-64). deBoar teaches that the prior art anti-CD40 antibodies mimic the effect of T-helper cells and thus can replace the T cell helper signal (column 2, lines 51-59). deBoar teaches "new" antibodies such as 5D12, 3C6 and 3A8 which differ from the prior art anti-CD40 antibodies in that the new antibodies inhibit the B-cell stimulatory response (column 2, lines 62-67). deBoar teaches S2C6 as an "old" antibody (in contrast to the "new" antibodies) which stimulates B-cell proliferation (column 17, lines 57-62, and the description for Figures 5 and 6). deBoar teaches that the "new" antibodies can inhibit stimulatory signals elicited by the "triggering" of CD40 with another antibody (column 18, lines 36-40). One of skill in the art would reasonably conclude that the "old" S2C6 antibody "triggers" CD40. deBoar teaches that the administration of humanized versions of the "new" antibodies would be efficacious in the treatment of antibody-mediated autoimmune diseases (column 3, lines 52-65 and column 4, lines 14-19).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make a humanized or chimerized version of S2C6 for the treatment cancer in a subject. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Melief et al regarding: the

administration of FGK45 as a CD40 activating antibody in a method of treating cancer, and the general teachings of Melief et al on the importance of anti-CD40 antibodies in combination with tumor specific peptides for the reversal of immunological tolerance to said tumor specific peptides; in addition to the teachings of Melief et al on the importance of "triggering" CD40 in vivo for the induction of tumor specific immunity; and the teachings of deBoar on the triggering of CD40 by the "old" S2C6 antibody. One of skill in the art would specifically select the S2C6 antibody as an antibody which would trigger CD40 in vivo and replace the required T-cell helper signal needed to induce immunity rather than tolerance to a specific antigen.

Claims 9, 21-24, 36, 47-54 and 69 specify that the binding of the molecule or protein increases the binding of the CD40 ligand to CD40 on the surface of B cells by 45%, and up to at least 65%. It is noted that none of the references teach that the binding of the S2C6 antibody or the humanized version thereof results in the increase in CD40 ligand binding to the CD40 receptor by at least 45%. It is noted that Bjorck et al (Immunology, 1994, Vol. 83, pp. 430-437, cited in a previous Office action) teach that soluble CD40 ligand and the S2C6 antibody synergize in inducing proliferation of B-cells (page 433, , column 1, bridging sentence, and Table 2 "Il-4 + S2C6 + gp39") which is consistent with increasing the binding of the ligand. Furthermore, this would be an inherent property of the claimed antibodies derived from S2C6 because the S2C6 antibody and the humanized or chimerized S2C6 antibody taught by the specification would bind toCD40 at the same epitope, and thus, the interaction of the CD40 ligand with CD40 would be effected by the same alteration in structure resulting from the binding of an antibody to the S2C6 epitope. Thus, it would be inherent that the humanized or chimeric antibody derived from S2C6 would increase the binding of CD40 ligand to CD40, because the process of humanization would not alter the epitope to which the humanized antibody binds and thus the impact of the binding of the humanized or chimerized antibody on the CD40 molecule would be determined by the binding of the antibody to the S2C6 epitope. Applicant has previously argues against the teachings of Bjorck et al stating that they taught away from the instant invention because of the results of the ELISA assay presented in Table 4, wherein it is indicated that S2C6 inhibits the binding of gp39 by 57.9%. This has been considered but not found persuasive. Table 2 of Bjorck et al teaches the synergism of gp39 and S2C6 in the proliferation of B cells: entries five and six indicate the uptake of tritiated thymidine

in B-cells resulting from contact with S2C6 at two different concentration, entries 9 and 10 indicate the uptake of tritiated thymidine in B-cells resulting from contact with gp39 at two different concentrations, entries 19 and 20 indicate the uptake of tritiated thymidine resulting from contact with both S2C6 and gp39. It is clear from this data that the resulting proliferation induced by the combination of S2C6 and gp39 is far in excess from that expected from an additive effect of S2C6 and gp39. Further, the results in Table 4 which indicate that S2C6 inhibits the biding of gp39 in the ELISA assay are not germane to the instant case. The results set forth in Table 2 are for the binding of S2C6 to CD40 on the cell surface, the results indicated for table 4 represent the binding of S2C6 and gp39 to the CD40-Ig fusion protein which was immobilized on the surface of the 96-well plate (page 431, second column, lines 3-12, under the heading "Epitope analysis"). Given that the results of the activation of cellular proliferation presented in Table 2 showed synergistic effects with the addition of S2C6 and gp39, one of skill in the art would reasonably conclude that ELISA data on the competition with binding to a CD40-Ig coated solid support does not accurately mimic CD40 receptor on a cell surface.

12. Claims 1-3, 6-9, 21-24, 34, 38, 39, 42-44, 47-66, 68-71, 74-76, 82 and 86-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over as applied to claims 1-3, 6-9, 21-24, 38, 39, 42-44, 47-66, 68-71, 74-76, 82 and 86-88 above, and further in view of Greenwood and Clark (Effector functions of human IgG, In:Protein engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, Clark, Ed., 1993, pp. 85-87). Claim 34 embodies the antibody of claim 3 which is not isotype IgG1. None of the aforementioned reference teaches antibodies which are not isotype IgG1. Greenwood and Clark teach that antibody variable genes can be expressed with different constant region genes, permitting production of matched sets of antibodies of different isotypes but with identical antigen specificity and single site affinity (page 86, lines 38-41).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make the antibody rendered obvious by the teachings of Melief et al and deBoar et al having any constant region. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Greenwood and

Clark on the preservation of antigen affinity and epitope binding of antibodies constructed to have the same variable regions but different constant regions.

13. Claims 1-3, 6-9, 21-25, 36, 38, 39, 42-44, 67, 47-71, 74-76, 82 and 86-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Funakoshi et al (Blood, 1994, Vol. 83, pp. 2787-2794, cited in a previous Office action) in view of Bjorck et al (Immunology, 1994, Vol. 83, pp. 430-437, cited in a previous Office action) and deBoar (U.S. 5,874,082) as evidenced by Unkun et al (Blood, 1990, Vol. 76, pp. 2449-2456, cited in a previous Office action). The specific embodiments of claims 1-3, 6-9, 21-24, 38, 39, 42-44, 47-66, 68-71, 74-76, 82 and 86-88 are set forth above.

Claim 25 embodies the pharmaceutical composition of any one of claims 21-24 further comprising CD40 ligand. Claim 67 embodies the pharmaceutical composition of claim 25 wherein the CD40 ligand is purified. Claim 36 is drawn to a pharmaceutical composition comprising in an amount effective for the treatment of prevention of cancer or an immune disorder.

Funakoshi et al teach that B-and T-cell malignancies can be arrested by exposure to stimuli that lead to activation in normal B or T cells. Funakoshi et al teach that anti-CD40 antibodies, which exert stimulatory responses on B-cell proliferation (page 2787, first column, under the heading "Antibodies") resulted in the inhibition of proliferation of lymphoma cells lines, and that cross linking of the antibody resulted in a greater growth inhibition (page 2788, second column, under the heading "Effects of anti-CD40 on human B-cell lymphoma proliferation in vitro"). Funakoshi et al teach that soluble CD40 ligand also inhibited lymphoma growth in vitro (pp.2788-2791, under the heading "Effects of soluble CD40 ligand on human B-cell lymphoma"). Funakoshi et al teach that the anti-CD40 antibodies administered to mice significantly inhibited the growth of transplanted human B-cell lymphomas (page 2791, first column, last full sentence). Funakoshi et al do not teach the administration of both the anti-CD40 antibody and the CD40 ligand. Funakoshi et al do not teach the humanized S2C6 antibody.

Unkun et al teach that chronic lymphocytic leukemias and non-Hodgkin's lymphomas express the CD40 antigen (abstract).

Bjorck et al teach that S2C6 synergizes with gp39 in the triggering of proliferation through the activation of the CD40 receptor. Table 2 of Bjorck et al teaches the synergism of gp39 and S2C6 in the proliferation of B cells: entries five and six indicate the uptake of tritiated thymidine in B-cells resulting from contact with S2C6 at two different concentration, entries 9 and 10 indicate the uptake of tritiated thymidine in B-cells resulting from contact with gp39 at two different concentrations, entries 19 and 20 indicate the uptake of tritiated thymidine resulting from contact with both S2C6 and gp39. It is clear from this data that the resulting proliferation induced by the combination of S2C6 and gp39 is far in excess from that expected from an additive effect of S2C6 and gp39.

DeBoar teaches that anti-CD40 antibodies known in the art prior to the disclosure (of DeBoar) have a stimulatory effect on human B cells (column 2, lines 45-46 and 62-64). DeBoar teaches that the prior art anti-CD40 antibodies mimic the effect of T-helper cells and thus can replace the T cell helper signal (column 2, lines 51-59). DeBoar teaches that the "new" antibodies can inhibit stimulatory signals elicited by the "triggering "of CD40 with another antibody (column 18, lines 36-40). Boar teaches that the administration of humanized versions of the "new" antibodies would be efficacious in the treatment of antibody-mediated autoimmune diseases (column 3, lines 52-65 and column 4, lines 14-19).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make a pharmaceutical composition comprising humanized or chimerized S2C6 antibody and gp39 for the treatment of lymphoma and leukemia One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Funakoshi et al on the induction of cell death in malignant B cells by the administration of a CD40 ligand or a anti-CD40 antibody which normal results in activation of proliferation on normal B-cells; the teachings of DeBoar on the activation of proliferation induced by S2C6 and the teachings of Bjorck et on the synergism of gp39 and S2C65 in the proliferation of B cells.

Applicant has previously argued against the teachings of Bjorck et al stating that they taught away from the instant invention because of the results of the ELISA assay presented in Table 4, wherein it is indicated that S2C6 inhibits the binding of gp39 by 57.9%. This has been considered but not found persuasive. Table 2 of Bjorck et al teaches the synergism of gp39 and

S2C6 in the proliferation of B cells: entries five and six indicate the uptake of tritiated thymidine in B-cells resulting from contact with S2C6 at two different concentration, entries 9 and 10 indicate the uptake of tritiated thymidine in B-cells resulting from contact with gp39 at two different concentrations, entries 19 and 20 indicate the uptake of tritiated thymidine resulting from contact with both S2C6 and gp39. It is clear from this data that the resulting proliferation induced by the combination of S2C6 and gp39 is far in excess from that expected from an additive effect of S2C6 and gp39. Further, the results in Table 4 which indicate that S2C6 inhibits the binding of gp39 in the ELISA assay are not germane to the instant case because said data is for the binding of S2C6 and gp39 to the CD40-Ig fusion protein which was immobilized on the surface of the 96-well plate (page 431, second column, lines 3-12, under the heading "Epitope analysis"). Given that the results of the activation of cellular proliferation presented in Table 2 showed synergistic effects with the addition of S2C6 and gp39, one of skill in the art would reasonably conclude that ELISA data on the competition with binding to a CD40-Ig coated solid support does not accurately mimic CD40 receptor on a cell surface.

14. Claims 1-9, 21-24, 38, 39, 42-44, 47-60, 62-66, 68-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francisco et al (The Journal of Biological Chemistry, 1997, Vol. 272, pp. 24165-24169, cited in a previous Office action) in view of Paulie et al (Cancer Immunology, Immunotherapy, 1985, Vol. 20, pp. 23-28, cited in a previous Office action) and DeBoar (U.S. 5,874,082) and Schlom (Molecular Foundations of Oncology, S. Broader, Ed., 1991, pp. 95-134). The specific embodiments of claims 1-3, 6-9, 21-24, 38, 39, 42-44, 47-66, 68-71, 74-76, 82 and 86-88 are set forth above.

Claim 4 is drawn to a molecule comprising SEQ ID NO:8, 9 and 10, which molecule binds CD40 and is a fusion protein. Claim 5 embodies the molecule of claim 4 , wherein said molecule comprises the amino acid sequence of bryodin fused to SEQ ID NO:7 and SEQ ID NO:2. Claim 89 embodies the molecule of claim 4 wherein he second molecule is bryodin. Claim 72 embodies the molecules of claims 1-3 and 69, respectively, wherein the molecule is conjugated to a therapeutic agent. Claim 79 embodies the molecule of claim 72 which is an antibody. Claims 73 embodies the molecule of claims 8, 9 and 44 which is conjugated to a therapeutic agent. Claim 77 embodies the molecules of claims 21 and 23 wherein said molecules

are conjugated to a chemotherapeutic agent. Claim 78 embodies the molecules of claims 22 and 24 wherein said molecules are conjugated to a chemotherapeutic agent.

Claim 80 is drawn to a molecule which comprises SEQ ID NO:7 and is a single chain Fv. Claim 81 embodies the molecule of claim 80 which is conjugated to a chemotherapeutic agent.

Claim 83 is drawn to a protein comprising an ammo acid sequence that comprises regions having at least 80% identity to SEQ ID NO:8, 9 and 10, which protein binds CD40 and is a single chain Fv. claim 84 embodies the molecule of claim 83 which comprises SEQ ID NO:8, 9 or 10. Claim 85 embodies the molecule of claim 83 which comprises at least 2CDR sequence selected from the group consisting of SEQ ID NO: 8, 9 or 10. Claim 90 embodies the molecule of claim 83 which is fused to bryodin.

Claim 91 embodies the molecule of claim 87 which is fused to bryodin.

Francisco et al teaches that the toxin bryodin fused to the sFv fragment of the G28.5 antibody which binds to CD40 is cytotoxic to a non-Hodgkin's lymphoma cell line, a multiple myeloma cell line , a b-cell leukemia and a Hodgkin's disease cell line. Francisco et al teach that all these cell lines express CD40. Francisco et al teach that because the single chain immunotoxin comprising bryodin was cytotoxic without the addition of a translocation domain, this is indicative that bryodin itself possesses said translocation domain (page 24169, first column, lines 3-15). Because bryodin kills cancer cells, it is concluded that bryodin is a chemotherapeutic agent. Francisco et al also teach that G28.5 fused to Pseudomonas endotoxin was toxic to lung, breast, colon and ovarian carcinoma cell in vitro (page 24168, Table I)

Paulie et al teach that the S2C6 antigen is found on bladder cancer cells and on B lymphocytes (abstract lines 15-19). Paulie et al teach that the S2C6 epitope is part of the CD40 receptor (abstract, lines 1-3).

deBoer teaches how to make humanized anti-CD40 antibodies. deBoer does not specifically make a humanized anti-CD40 S2C6 antibody.

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of murine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the

answer to this problem is the humanization of the murine antibodies (pages 97-98, bridging paragraph). Schlom teaches that single chained antibodies and Fab antibody fragments have increased ability to penetrate through tumor masses in contrast to whole antibodies (page 119, second column first paragraph under the heading "Single Chain Antigen Binding Proteins").

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to treat B cell malignancies by the administration of a humanized S2C6 antibody conjugated or fused to bryodin, and to treat bladder, lung and ovarian carcinomas by the administration of a humanized S2C6 antibody fused to Pseudomonas endotoxin, wherein the S2C6 antibody was a tetravalent full antibody or a single chain Fv fragment. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Francisco et al on the cytotoxicity of bryodin fused to anti-CD40 antibodies on B cell malignancies and the teachings of Paulie et al on the presence of the S2C6 epitope on B lymphocytes. One of skill in the art would reasonably conclude that cancer cells which overexpress CD40 will be bound by the molecules, proteins and antibodies derived from the S2C6 antibody, and that the translocation domain of bryodin will allow for internalization of bryodin into the cytoplasm of the cancer cell.

15. Applicant argues that Francisco taught against the instant invention because Francisco taught that the bryodin fusions with the G28.5 antibodies were not toxic to carcinoma cells and that there is no suggestion of a therapeutic use of S2C6-like molecules. This has been considered but not found persuasive It is well known in the art that antibodies can specifically target cell types by binding to ligands which are expressed on said cell type. Thus, it would be obvious to one of skill in the art that bryodin fusion proteins targeted to the CD40 antigen would be toxic on hematological malignancies, whereas pseudomonas exotoxin fusion proteins targeted to the CD40 antigen would be toxic to lung, bladder or ovarian carcinoma cells. The S2C6 antibody was taught by Paulie to bind to the S2C6 epitope on CD40. Further, it would be expected that a single chain immunotoxin, such as the Fv derived from S2C6 fused to bryodin would enter a cell expressing the CD40 receptor because bryodin itself has a translocation domain. It would also be expected that pseudomonas endotoxin conjugated or fused to S2C6

would be toxic to carcinoma cells because said endotoxin is toxic to carcinoma cell when delivered via the G28.5 antibody which binds to the CD40 receptor.

16. Applicant argues on page 5 of the instant response that the examiner was inadvertently using hindsight to reconstruct the obviousness rejection, without considering the state of the art at the time of filing . This has been considered but not found persuasive. At the time of filing of the instant application, the construction of humanized and chimerized antibodies for the avoidance of anti-globulin responses in vivo was routine. Further, at the time of filing it was recognized that the S2C6 antibody activated the CD40 receptor, in opposition to the antibodies taught by DeBoar which were sought after as antagonistic antibodies. Melief et al teach that the administration of CD40-binding molecules enhances the efficacy of anti-cancer vaccines comprising tumor specific peptides. Melief set forth FGK45 as a CD40 activating antibody. Further, it was known that anti-CD40 antibodies, which exert stimulatory responses on B-cell proliferation resulted in the inhibition of proliferation of lymphoma cells lines as taught by Funakoshi et al. DeBoar teaches "new" antibodies which differ from the prior art anti-CD40 antibodies in that the new antibodies inhibit the B-cell stimulatory response. DeBoar teaches S2C6 as an "old" antibody, (in contrast to the "new" antibodies) which stimulates B-cell proliferation. Thus, DeBoar et al identified S2C6 antibody as exerting a stimulatory response of B-cell proliferation by virtue of comparison between the S2C6 antibody with the "new" antibodies. Clearly, the prior art at the time of filing had identified anti-CD40 antibodies which activate the CD40 receptor and stimulate B-cell proliferation as having therapeutic efficacy. DeBoar teaches that S2C6 is an anti-CD40 antibody which activates the CD40 receptor and stimulates B-cell proliferation. thus, it would be obvious to humanize the S2C6 antibody to administer for therapeutic efficacy against lymphoma cells and in vaccines with tumor cell antigens.

17. All other rejections and objections as set forth in Paper No. 20 are withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (571) 272-0828. The examiner can normally be reached on Monday through Friday from 9 am to 6:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at 703-308-4357.

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01/17/04